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The Safety and Efficacy of Tocilizumab in Older Adult Critically Ill Patients with Coronavirus Disease 2019 (COVID-19): A Multi-center, Cohort Study

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- Highlights:

  - The hyperinflammatory stage in COVID is characterized by surges of IL-6
  - The role of tocilizumab (TCZ) (IL-6 inhibitor) in COVID patients is controversial
  - TCZ have immunosuppressive effects which can be dubious in older COVID-19 patients
  - TCZ exhibited less in-hospital mortality but similar 30-d mortality in our study
  - No difference between groups in the incidence of secondary infections in our study

The Safety and Efficacy of Tocilizumab in Older Adult Critically Ill Patients with Coronavirus Disease 2019 (COVID-19): A Multi-center, Cohort Study

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Abstract

Background: Evidence supports Tocilizumab (TCZ) benefit and safety in adult patients with severe COVID-19. However, its effectiveness in critically ill older adult patients remains questionable. Thus, the study aimed to evaluate the safety and efficacy of TCZ in older critically ill patients with COVID-19.

Method: A multicenter, retrospective study for all critically ill older adults (aged ≥ 65 years old) with confirmed COVID-19 infection and admitted to the intensive care units. Eligible patients were categorized into two groups based on TCZ use during ICU stay (Control vs. TCZ). Propensity score matching was used (1:1 ratio) based on the selected criteria. The primary outcome was in-hospital mortality.

Results: A total of 368 older adults critically ill patients were included in the study. Fifty-one patients (13.8%) received TCZ. The in-hospital mortality was lower in the TCZ treated group HR (0.41 [95% CI 0.22-0.76], p-value =0.005). Patients who received TCZ had a lower odd of respiratory failure requiring mechanical ventilation OR (0.32 [95% CI 0.10-0.98]), p-value=0.04). No statistically significant differences were found between the two groups for 30-days mortality, ventilator-free days, length of stay, and complications during ICU stay.

Conclusion: TCZ use in older adults critically ill patients with COVID-19 is associated with lower in-hospital mortality and similar safety profile.

Keywords

COVID-19, SARS-CoV-2, Tocilizumab, Older adult, mortality, respiratory failure

Introduction

Since the novel severe acute respiratory syndrome coronavirus (SARS-CoV-2) emergence in 2019(Huang et al., 2020), coronavirus disease 2019 (COVID-19) has caused more than four million deaths globally.(Organization, 2021) COVID-19 pneumonia can progress to acute respiratory distress syndrome (ARDS), multiorgan dysfunction, or death [3]. This progression may be attributed to the body's inflammatory response exacerbating inflammatory mediators such as cytokines and chemokines, leading to cytokine storm.(Que et al., 2022) Therefore, many treatment modalities such as antiviral therapy, antibiotic therapy, immuno-modulating agents, and corticosteroids have been investigated to mitigate COVID-19 symptoms, reduce disease progression, and ultimately prevent mortality.(Gordon et al., 2021; Shaffer, 2020; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021)

Critically ill patients with severe COVID-19 exhibit elevated inflammatory markers, including interleukin-6 (IL-6).(Rizvi and Gallo De Moraes, 2021) Therefore, many studies have investigated the use of IL-6 targeting immunomodulators to treat COVID-19.(Gordon et al., 2021; Rizvi and Gallo De Moraes, 2021; Stone et al., 2020; K. Al Sulaiman et al., 2021; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) A randomized controlled trial by the RECOVERY Collaborative group demonstrated tocilizumab's (TCZ) effectiveness in reducing mortality and improving clinical outcomes in hospitalized patients with COVID-19.(Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) A systematic review and meta-analysis included 17 observational studies that compared TCZ with systemic steroid versus standard of care in patients with severe

COVID-19 reported a lower mortality rate in patients receiving TCZ.(Alkofide et al., 2021) Moreover, a recent systematic review and meta-analysis including 52 studies confirmed TCZ mortality benefits in the intensive care unit (ICU) and non-ICU patients regardless of the use of systemic corticosteroids, but TCZ did not significantly reduce mortality in the included observational studies.(Kyriakopoulos et al., 2021)

Even though most evidence supports the efficacy of TCZ use in patients with severe COVID-19 (Van den Eynde et al., 2021; Gordon et al., 2021; Kimmig et al., 2020; Kyriakopoulos et al., 2021; Mahale et al., 2020; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021), its effectiveness, specifically in patients with COVID-19 aged 65 years or older who are at higher risk of mortality, remains questionable.(Bhatraju et al., 2020; Grasselli et al., 2020) Older adult patients admitted to the ICU with COVID-19 have a higher number of comorbidities and a higher risk of death in the ICU.(Grasselli et al., 2020) A retrospective study conducted by our group have found that the overall ICU mortality within 30 days was 42.3% and up to 40% of included patients were ≥65 years old but we did not assess the use of TCZ in the previous study.(K. A. Al Sulaiman et al., 2021) While the RECOVERY trial which included both ICU and non-ICU patients reported mortality benefits with TCZ use in older adult patients (≥ 70 <80 years old) a RR (95% CI) of 0.83 (0.72−0.94) this group only represented 24% of the included patients at baseline.(Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) Another two-center study that included critically ill patients with COVID-19 conducted by our group compared the effectiveness and safety of two TCZ dosing regimens in adult above 18 years with a mean age of 59.0 (SD ± 12.8).(K. Al Sulaiman et al., 2021) Yet, most of the previously conducted studies investigated TCZ efficacy and safety, focusing on adults aged 18 or above with none of these studies addressing TCZ's benefit and risk in high-risk populations such as older adults [5,8,10,12–14].(Alkofide et al., 2021; Van den Eynde et al., 2021; Kimmig et al., 2020; Mahale et al., 2020; Shaffer, 2020; Stone et al., 2020) Therefore, this study aims to compare the safety and efficacy of TCZ versus control in critically ill older adult patients (aged ≥ 65 years old) with COVID-19.

Methods

Study Design

This study was a multicenter, retrospective cohort including critically ill older adult patients (aged ≥ 65 years old) with confirmed COVID-19 admitted to the intensive care units (ICUs) at four hospitals in Saudi Arabia from March 01, 2020, until March 31, 2021. All patients were observed until they were discharged from the hospital or died during their stay, whichever occurred first. Due to the study's retrospective observational nature, informed consent from study participants was waived. This project was approved by King Abdullah International Medical Research Center (KAIMRC) (IRB number NRC21R.434.10) as the primary site.

Study Participants

We included all older adult patients (age ≥ 65 years) admitted to the ICUs with confirmed COVID-19. Patients were diagnosed with COVID-19 using Reverse Transcriptase-Polymerase Chain Reaction (RT-PCR) nasopharyngeal or throat swabs. Patients were excluded if the ICU length of stay (LOS) ≤ one day, died within the first 24 hours of ICU admission, were labeled as "Do-Not-Resuscitate," received TCZ before ICU admission or after 24 hours of ICU admission (Figure 1). Eligible patients were then categorized based on TCZ use during ICU stay into two groups (Control vs. TCZ). TCZ has been approved for the treatment in patients with severe COVID-19 in Saudi Arabia, according to the Saudi Ministry of Health (MOH) guidelines for COVID-19 management in critically ill patients. (Health, n.d.) TCZ was administered as a single dosage of 4–8 mg/kg based on the actual body weight (maximum 800 mg) through IV infusion; a repeated dose was given based on clinical assessment. (Health, n.d.)

Study Settings

The study was conducted at four hospitals representing three regions in Saudi Arabia: King Abdulaziz Medical City (Riyadh), King Abdulaziz University Hospital (Jeddah), King Abdullah bin Abdulaziz University Hospital (Riyadh), and King Salman Specialist Hospital (Hail). The primary center was King Abdulaziz Medical City.

Data Collection

Each patient's data were collected and handled using King Abdullah International Medical Research Center's (KAIMRC) Research Electronic Data Capture (REDCap®) version 9.1.2 software. The following demographic and laboratory data were collected: comorbidities, vital signs. In addition to renal profile (i.e., estimated glomerular filtration rate (eGFR)), liver function tests (LFTs) (i.e., total bilirubin, ALT, AST), coagulation profile (i.e., INR, aPTT, platelets count), and inflammatory markers (ferritin, D-dimer, and C-reactive protein (CRP)) within 24 hours of ICU admission. Moreover, severity score baseline (i.e., Acute Physiology and Chronic Health Evaluation II (APACHE II) and Sequential Organ Failure Assessment (SOFA)), Glasgow Coma Score (GCS), acute kidney injury (AKI), prone positioning, the needs for mechanical ventilation (MV) and MV parameters (e.g., PaO2/FiO2 ratio, FiO2 requirement) within 24 hours of ICU admission were documented. In addition, early use of corticosteroids and pharmacological venous thromboembolism (VTE) prophylaxis were recorded for the eligible patients

Study Outcomes

The study aims to assess the efficacy and the safety of TCZ in critically ill older adult patients (aged ≥ 65 years old) with COVID-19. The primary outcome was the in-hospital mortality compared between patients who received TCZ versus the control group during the ICU stay. The secondary outcomes were the 30-day mortality, hospital LOS, ICU LOS, ventilator-free days (VFDs), and ICU-related complication(s) during the ICU stay (i.e., acute kidney injury, acute liver injury, secondary fungal infection, respiratory failure requiring MV, and the use of inotropes/vasopressors as supportive measures).

The primary outcome was in-hospital mortality which was defined as death occurring for any cause during hospital stay; patients who were discharged from the hospital alive were presumed to survive. The remaining secondary outcomes definitions are provided in the Additional file (**Table S1)**

Statistical Analysis

We presented numerical variables (continuous variables) as mean and standard deviation (SD), or median and lower quartile (Q1) and upper quartile (Q3), as appropriate and categorical variables as number (percentage). The normality assumptions were assessed for all numerical variables using the Shapiro-Wilk test and graphical representations using histograms and Q-Q plots. Model fit was assessed using the Hosmer-Lemeshow goodness-of-fit test.

Baseline characteristics and outcome variables were compared between the two study groups for statistical differences. For categorical variables, we used the Chi-square or Fisher's exact test. We compared the normally distributed continuous variables using student t-test and other non-normally distributed continuous variables with the Mann-Whitney U test.

Multivariable Cox proportional hazards regression analyses were performed for the 30-day and in-hospital mortality. Multivariable regression analysis and negative binomial regression were used for the other outcomes considered in this study. The odds ratios (OR), hazard ratio (HR), or estimates with the 95% confidence intervals (CI) were reported as appropriate. Regression analysis was done by considering PS score as one of the covariates in the model. No imputation was made for missing data as the cohort of patients in our study was not derived from random selection. We considered a *P* value of < 0.05 statistically significant and used SAS version 9.4 for all statistical analyses.

Propensity score matching procedure (Proc PS match) (SAS, Cary, NC) was used to match patients who received TCZ (active group) to patients who did not (control group) based on patient's age, APACHE II score, use of systemic corticosteroids, and AKI status within 24 hours of ICU admission. A greedy nearest neighbor matching method was used in which one patient who received TCZ matched with one patient who did not, which eventually produced the smallest within-pair difference among all available pairs with treated patients. Patients were matched only if the difference in the logits of the propensity scores for pairs of patients from the two groups was less than or equal to 0.5 times the pooled estimate of the standard deviation.

Results

A total of 1094 patients admitted to the ICU were screened; 368 older adult patients (aged ≥ 65 years old) were eligible based on the selected criteria in Figure 1. Of those, 51 patients (13.8%) received TCZ during their ICU stay. After propensity score (PS) matching (1:1 ratio), 94 patients were included based on predefined criteria. All included patients received TCZ within 24 hours of ICU admission. Twenty-four patients (47%) received a single dose of TCZ.

Demographic and Clinical Characteristics

Before PS matching, the majority of patients were male (65.8 %), with a mean age of 75.6 (SD 7.88). The commonest underlying comorbidities in our patients were hypertension (70.7 %), diabetes mellitus (68.2 %), and dyslipidemia (26.5 %) (Table 1.) There were some notable differences in the baseline characteristics between the two groups before PS matching. Patients who received TCZ were younger, received more systemic corticosteroids within 24 hours of ICU admission, had higher C-reactive protein (CRP) and ferritin levels at baseline. After adjusting PS matching based on the selected criteria, all baseline, and demographic characteristics were similar between the two groups except for diabetes mellitus which was more prevalent in the control group, as presented in Table 1.

Outcomes

In-Hospital and 30-Day Mortality

In a crude analysis, there was a significant difference in the in-hospital (37.8% vs. 67.4 %, p-value= 0.005) and 30-day mortality (34.8% vs. 56.5%, p-value=0.04) in patients who received TCZ compared to the control respectively. Additionally, after the cox proportional hazards regression analysis, the in-hospital mortality was significantly lower in patients who received TCZ than those who did not (HR 0.41; 95% CI 0.22, 0.76, p-value =0.005). Moreover, patients who received TCZ have lower deaths within 30 days of admission than patients who did not receive TCZ; however, this finding did not reach statistical significance (HR 0.66; 95% CI 0.35, 1.24, p-value= 0.19) as shown in Table 2**.** In a Kaplan-Meier curve, the administration of tocilizumab was associated with better survival outcomes in elderly COVID-19 patients as shown in Figure. 2.

Ventilator Free Days & Length of Stay

The mean VFD was longer in crude analysis toward patients who received TCZ with a mean difference of 12.3 (±13.3) days compared to 8.8 (±12.5) days in the control group. However, it failed to reach the statistically significant difference after regression analysis with a beta coefficient (95%CI): 32 (-0.70, 1.34), p-value=0.54. **(Table 2).**

The ICU and LOS were not statistically significant in patients who received TCZ compared to the control group (12.5 (8.0, 18.0) vs. 10.0 (3.0, 15.0) p-value 0.37), (22 (14.5, 36.0) vs. 25 (10.0, 40.0), p-value 0.84), respectively. Moreover, there was no significant difference in ICU LOS (beta coefficient, 95% CI 0.36 (-0.17, 0.89), p-value=0.18) nor hospital LOS (beta coefficient, 95% CI 0.20 (-0.30, 0.71), p-value=0.43) between the two groups after regression analysis **(Table 2).**

Complications During ICU Stay

Patients who received TCZ had a lower odd of respiratory failure requiring MV (OR (95%CI): 0.32 (0.10, 0.98), p-value=0.04). Additionally, other complications during ICU such as acute kidney injury, liver injury, secondary fungal infection were lower than the control; however, these results did not reach statistical significance **(Table 3).**

Discussion

This multicenter retrospective study found that the in-hospital mortality rate was significantly lower in older adult patients who received TCZ than those who did not. However, the 30-day mortality was numerically lower in the TCZ group but did not reach a statistically significant difference. On the other hand, the in-hospital mortality was statistically significantly lower in elderly patients who received TCZ, which might be due to a longer follow-up period that may detect other hospital-related complications. Similarly, the odds of respiratory failure requiring MV were significantly lower in older adult patients with COVID-19 who received TCZ during the ICU stay.

In our study, older adult patients with COVID-19 who received TCZ had a significant reduction in the in-hospital mortality. This result was consistent with previous studies' findings showing survival benefit following TCZ administration among patients with COVID-19. (Van den Eynde et al., 2021; Gordon et al., 2021; Hermine et al., 2021; Kimmig et al., 2020; Salama et al., 2021; Soin et al., 2021; Stone et al., 2020; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) In our previous study increasing the number of TCZ doses showed no significant difference in mortality rather it showed higher odds of pneumonia in patients who received multiple TCZ doses. (K. Al Sulaiman et al., 2021) However, all these reports included adult patients with COVID-19 not specific to older adult patients. Unlike adult patients, older adult patients usually have multiple chronic conditions that complicate COVID-19 diseases outcome or progression, management and increase their risk of mortality. (Health, n.d.; Salama et al., 2021) The mean age of patients included in our study was 73.2 years old which indicated an older population compared to the mean age included in the REMAP-CAP and RECOVERY trials at 61.5 and 63.3, respectively.

(Stone et al., 2020; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) Even though our patients had a higher CRP level and a lower PaO2/FiO2 at baseline than those included in other studies, our mortality benefit is consistent with the previous studies. (Grasselli et al., 2020; Stone et al., 2020; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) All study patients in our cohort received their first dose of TCZ during their first day of ICU admission, which could justify the reduction of in-hospital mortality as early use might target the peak of the cytokine's releases; this is aligns to some reported data from previous studies. Time to the first dose of TCZ in RECOVERY and REMAP-CAP trials was relatively consistent to our study with a median of 2 and 1.2 days, respectively. (Stone et al., 2020; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021)

Patients with COVID-19 reported having high levels of IL-6 and other inflammatory biomarkers, such as cytokines, MIP1A, and TNF-α. (Aldhaeefi et al., 2021; Bhatraju et al., 2020; Grasselli et al., 2020; Soin et al., 2021) The mortality benefit of TCZ in patients with severe COVID-19 remains debatable. (Aldhaeefi et al., 2021; Alkofide et al., 2021; Bhatraju et al., 2020; Kyriakopoulos et al., 2021; Soin et al., 2021) This mortality reduction uncertainty could be explained by a theory suggesting this hyperinflammatory immune response represents a natural and possibly beneficial host response against infection and suggestive of macrophage activation. (Aldhaeefi et al., 2021; Bhatraju et al., 2020; Grasselli et al., 2020; Soin et al., 2021) In support of this theory, Hermine O et al. failed to show a mortality reduction among COVID-19 patients receiving TCZ despite including patients with moderate disease (WHO-CPS score of 5), with a lower CRP than our patients, and early administration of TCZ. (Hermine et al., 2021)

Moreover, our patients had higher rates of MV and comorbidities than those included in the COVINTOC trial, which also failed to show a mortality benefit of the TCZ.(Soin et al., 2021) Similarly, Salama C et al. and Stones JH et al. failed to demonstrate a mortality benefit of the TCZ despite that 83% and 64.7% of the study's population were non critically ill patients, respectively. (Alkofide et al., 2021; Kyriakopoulos et al., 2021) Our findings suggest that TCZ could reduce respiratory failure requiring MV and disease progression in high-risk patients such as older adult patients with COVID-19. This finding is contrary to the RECOVERY trial in which TCZ use did not result in a reduction of respiratory failure requiring MV among patients older than 80 years old included.(Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) However, several studies concurred with our findings and reported that TCZ use is effective in preventing clinical worsening, disease progression, and the need for MV for patients at a higher risk of clinical worsening despite including mild, moderate, and severe COVID-19 patients. However, these results were uncertain about TCZ's effectiveness in preventing disease progression among older adult patients with COVID-19, given the heterogeneity of the patient population included in these studies. (Hermine et al., 2021; Salama et al., 2021; Sciascia et al., 2020; Stone et al., 2020; Toniati et al., 2020; Xu et al., 2020)

Additionally, patients treated with TCZ in this study had a trend of prolonged ICU and hospital LOS. This finding was consistent with the RECOVERY trial among patients older than 80 years old. (Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) Both mortality benefit and the improvement in the respiratory failure among our patients might explain the prolonged ICU and hospital LOS. Additionally, having patients in a strictly controlled and isolated environment was one of the precautionary steps to avoid spreading infections during COVID-19 pandemic outside the hospitals.

In regard to the ICU complications, there were no significant differences in the two study groups. TCZ is a potent immunomodulator that works through competitive inhibition of IL-6 binding to its receptor. (K. Al Sulaiman et al., 2021; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021) A major concern with administering such therapy among patients with COVID-19 patients is the serious secondary infections. Several studies have reported more serious secondary infections following TCZ administration [8,10,12,15]. (Alkofide et al., 2021; Bhatraju et al., 2020; Kimmig et al., 2020; Stone et al., 2020) In contrast to these studies, we found a non-significant difference in the rate of secondary fungal infections. Several studies reported similar findings regarding secondary infections with TCZ vs. standard of care. (Aldhaeefi et al., 2021; Kyriakopoulos et al., 2021; Sciascia et al., 2020; Soin et al., 2021; Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial., 2021)

As far as we know, this is one of the first multicenter studies that investigated the efficacy and safety of TCZ in critically ill older adult patients with COVID-19. In addition, propensity score matching was used to eliminate a greater portion of bias and create a balanced dataset. However, the study is not free of limitations. First, it was a retrospective study that included a relatively small sample size. Second, short follow-up duration may limit capturing further secondary infections or long-term complications. Lastly, our study might be underpowered to detect a difference in long term outcomes

Conclusion

This study shows that TCZ administration among critically ill older adults with COVID-19 resulted in reduced in-hospital mortality without a significant increase of secondary infections or other ICU complications. Further robust randomized clinical trials evaluating the safety and efficacy of TCZ among older critically ill patients with COVID-19 are needed to confirm our findings.

Abbreviation (s)

ICUs: Intensive care units**, COVID-19:** Coronavirus disease**, MV:** Mechanical ventilation**, TCZ:** Tocilizumab**, LOS:** Length of Stay**, APACHE II:** Acute Physiology and Chronic Health Evaluation II, SOFA: Sequential Organ Failure Assessment, **Q1,Q3**: 1st interquartile and 3rd interquartile, **eGFR**: Glomerular filtration rate , **AKI**: Acute Kidney Injury , **MV**: Mechanical Ventilation, **INR**: International normalized ratio, **aPTT**: activated partial thromboplastin time, **C-RP**: C-reactive protein, **CPK**: Creatine phosphokinase, **PaO2/FiO2** arterial oxygen tension / fraction of inspired oxygen

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Author contributions

All authors contributed to data collections, analysis, drafted, revised, and approved the manuscript's final version. All authors critically revised the manuscript, agreed to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

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Availability of data and material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethics approval and consent to participate

The study was approved by King Abdullah International Medical Research Center (KAIMRC), Riyadh, Saudi Arabia (Ref.#. NRC21R.434.10). Throughout the study, participants' confidentiality was rigorously preserved by utilizing an anonymous unique serial number for each individual and confining data to just the investigators. Informed consent was not required due to the research method, which was following the policies of the governmental and local research institutes.

Consent for publication

Not applicable.

Competing interests

No author has a conflict of interest in this study.

Supplementary information

Additional file 1: Table S1 Secondary outcomes definitions

Figure 1: Flow chart of patients admitted to the ICU (before propensity score match)

Figure 2: Overall survival plot analysis.

References

Aldhaeefi M, Tahir Z, Cote DJ, Izzy S, El Khoury J. Comorbidities and Age Are Associated With Persistent COVID-19 PCR Positivity. Front Cell Infect Microbiol 2021;11:650753. https://doi.org/10.3389/fcimb.2021.650753.

Alkofide H, Almohaizeie A, Almuhaini S, Alotaibi B, Alkharfy KM. Tocilizumab and Systemic Corticosteroids in the Management of Patients with COVID-19: A Systematic Review and Meta-Analysis. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2021;110:320–9. https://doi.org/10.1016/j.ijid.2021.07.021.

Bhatraju PK, Ghassemieh BJ, Nichols M, Kim R, Jerome KR, Nalla AK, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. N Engl J Med 2020;382:2012–22. https://doi.org/10.1056/NEJMoa2004500.

Van den Eynde E, Gasch O, Oliva JC, Prieto E, Calzado S, Gomila A, et al. Corticosteroids and tocilizumab reduce in-hospital mortality in severe COVID-19 pneumonia: a retrospective study in a Spanish hospital. Infect Dis (London, England) 2021;53:291–302. https://doi.org/10.1080/23744235.2021.1884286.

Gordon AC, Mouncey PR, Al-Beidh F, Rowan KM, Nichol AD, Arabi YM, et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med 2021;384:1491–502. https://doi.org/10.1056/NEJMoa2100433.

Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline Characteristics and Outcomes of 1591 Patients Infected With SARS-CoV-2 Admitted to ICUs of the Lombardy Region, Italy. JAMA 2020;323:1574–81. https://doi.org/10.1001/jama.2020.5394.

Health S ministry of. Saudi MoH Protocol for Patients with Suspected of/Confirmed with COVID-

19. Supportive care and antiviral treatment of suspected or confirmed COVID-19 infection (version 3.1), August 19th, 2021. n.d.

Hermine O, Mariette X, Tharaux P-L, Resche-Rigon M, Porcher R, Ravaud P. Effect of Tocilizumab vs Usual Care in Adults Hospitalized With COVID-19 and Moderate or Severe Pneumonia: A Randomized Clinical Trial. JAMA Intern Med 2021;181:32–40. https://doi.org/10.1001/jamainternmed.2020.6820.

Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet (London, England) 2020;395:497–506. https://doi.org/10.1016/S0140-6736(20)30183-5.

Kimmig LM, Wu D, Gold M, Pettit NN, Pitrak D, Mueller J, et al. IL-6 Inhibition in Critically Ill COVID-19 Patients Is Associated With Increased Secondary Infections. Front Med 2020;7:583897. https://doi.org/10.3389/fmed.2020.583897.

Kyriakopoulos C, Ntritsos G, Gogali A, Milionis H, Evangelou E, Kostikas K. Tocilizumab administration for the treatment of hospitalized patients with COVID-19: A systematic review and meta-analysis. Respirology 2021;26:1027–40. https://doi.org/10.1111/resp.14152.

Mahale N, Rajhans P, Godavarthy P, Narasimhan VL, Oak G, Marreddy S, et al. A Retrospective Observational Study of Hypoxic COVID-19 Patients Treated with Immunomodulatory Drugs in a Tertiary Care Hospital. Indian J Crit Care Med Peer-Reviewed, Off Publ Indian Soc Crit Care Med 2020;24:1020–7. https://doi.org/10.5005/jp-journals-10071-23599.

Organization WH. WHO Coronavirus Disease (COVID-19) Dashboard 2021. https://covid19.who.int/ (accessed October 5, 2021).

Que Y, Hu C, Wan K, Hu P, Wang R, Luo J, et al. Cytokine release syndrome in COVID-19: a major mechanism of morbidity and mortality. Int Rev Immunol 2022;41:217–30. https://doi.org/10.1080/08830185.2021.1884248.

Rizvi MS, Gallo De Moraes A. New Decade, Old Debate: Blocking the Cytokine Pathways in Infection-Induced Cytokine Cascade. Crit Care Explor 2021;3:e0364. https://doi.org/10.1097/CCE.0000000000000364.

Salama C, Han J, Yau L, Reiss WG, Kramer B, Neidhart JD, et al. Tocilizumab in Patients Hospitalized with Covid-19 Pneumonia. N Engl J Med 2021;384:20–30. https://doi.org/10.1056/NEJMoa2030340.

Sciascia S, Aprà F, Baffa A, Baldovino S, Boaro D, Boero R, et al. Pilot prospective open, single-arm multicentre study on off-label use of tocilizumab in patients with severe COVID-19. Clin Exp Rheumatol 2020;38:529–32.

Shaffer L. 15 drugs being tested to treat COVID-19 and how they would work. Nat Med 2020. https://doi.org/10.1038/d41591-020-00019-9.

Soin AS, Kumar K, Choudhary NS, Sharma P, Mehta Y, Kataria S, et al. Tocilizumab plus standard care versus standard care in patients in India with moderate to severe COVID-19-associated cytokine release syndrome (COVINTOC): an open-label, multicentre, randomised, controlled, phase 3 trial. Lancet Respir Med 2021;9:511–21. https://doi.org/10.1016/S2213-2600(21)00081-3.

Stone JH, Frigault MJ, Serling-Boyd NJ, Fernandes AD, Harvey L, Foulkes AS, et al. Efficacy of Tocilizumab in Patients Hospitalized with Covid-19. N Engl J Med 2020;383:2333–44. https://doi.org/10.1056/NEJMoa2028836.

Al Sulaiman K, Aljuhani O, Bin Salah K, Korayem GB, Eljaaly K, Al Essa M, et al. Single versus multiple doses of Tocilizumab in critically ill patients with coronavirus disease 2019 (COVID-19): A two-center, retrospective cohort study. J Crit Care 2021;66:44–51. https://doi.org/10.1016/j.jcrc.2021.08.007.

Al Sulaiman KA, Aljuhani O, Eljaaly K, Alharbi AA, Al Shabasy AM, Alsaeedi AS, et al. Clinical features and outcomes of critically ill patients with coronavirus disease 2019 (COVID-19): A multicenter cohort study. Int J Infect Dis IJID Off Publ Int Soc Infect Dis 2021;105:180–7. https://doi.org/10.1016/j.ijid.2021.02.037.

Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet (London, England) 2021;397:1637–45. https://doi.org/10.1016/S0140-6736(21)00676-0.

Toniati P, Piva S, Cattalini M, Garrafa E, Regola F, Castelli F, et al. Tocilizumab for the treatment of severe COVID-19 pneumonia with hyperinflammatory syndrome and acute respiratory failure: A single center study of 100 patients in Brescia, Italy. Autoimmun Rev 2020;19:102568. https://doi.org/10.1016/j.autrev.2020.102568.

Xu X, Han M, Li T, Sun W, Wang D, Fu B, et al. Effective treatment of severe COVID-19 patients with tocilizumab. Proc Natl Acad Sci U S A 2020;117:10970–5. https://doi.org/10.1073/pnas.2005615117.

Figure 1. Flow chart of patients admitted to the ICU (before propensity score match)

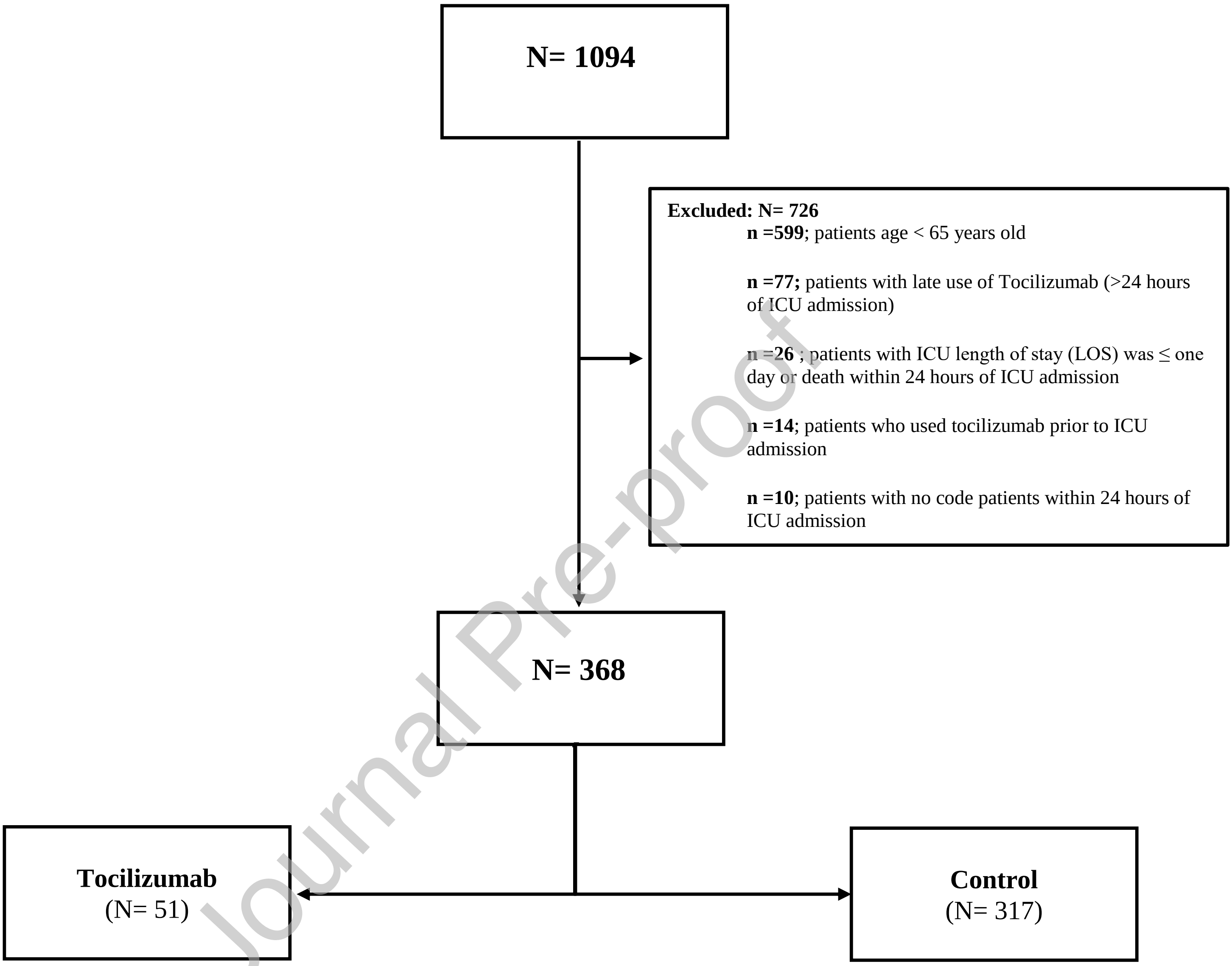

Figure 2: Overall survival plot during the hospital stay comparing patients who received Tocilizumab versus the control group

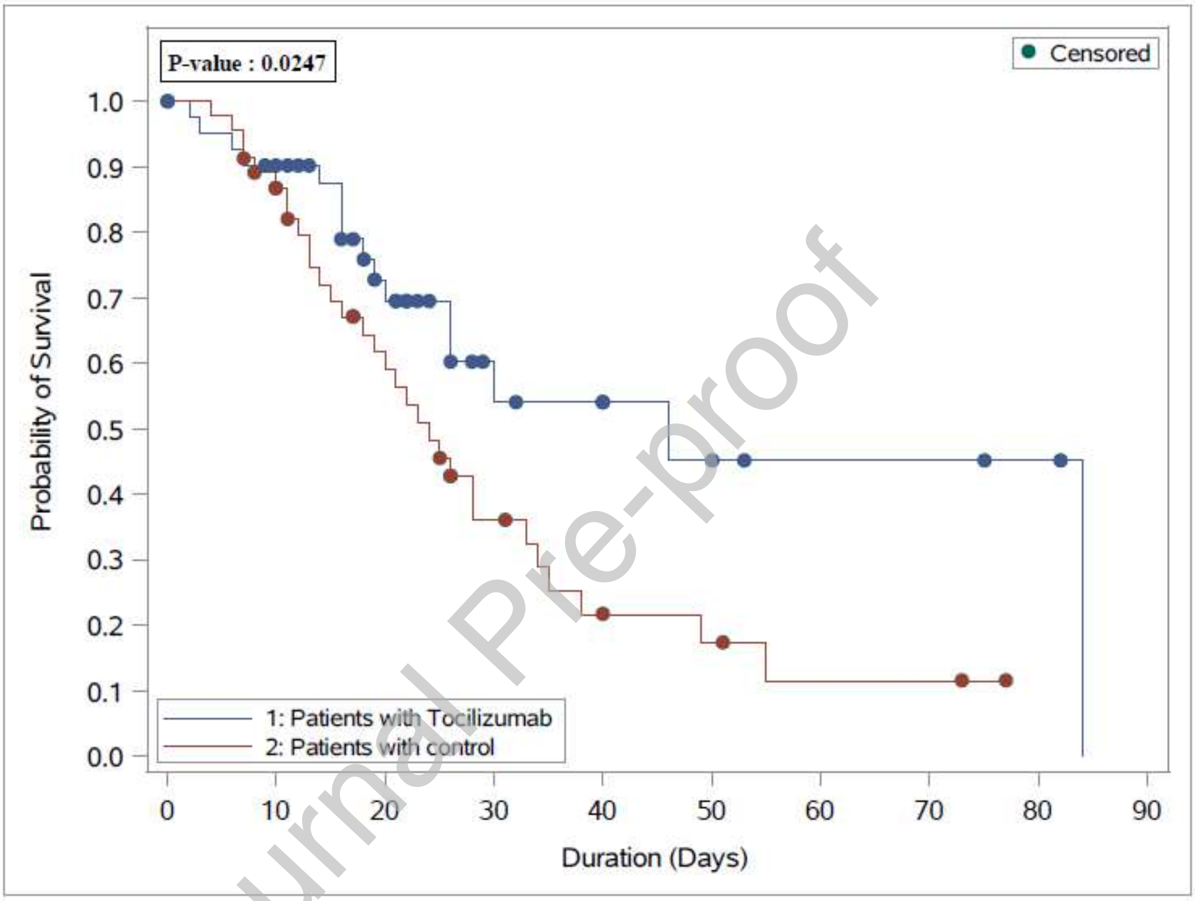

Table 1. Baseline characteristics

	Before propensity score (PS) adjustment				After propensity score (PS) adjustment			
	Overall (N=368)	**Control (N=317)**	**Tocilizumab (N=51)**	**P-value**	**Overall (N=94)**	**Control (N=47)**	**Tocilizumab (N=47)**	**P-value**
Age (Years), Mean (SD)	75.6 (7.88)	76.0 (7.98)	73.4 (6.95)	**0.012^**	73.1 (6.71)	73.0 (6.45)	73.2 (7.02)	0.994^
Gender – Male, , n (%)	237 (65.8)	201 (65)	36 (70.6)	0.44^^	65 (69.9)	32 (69.6)	33 (70.2)	0.945^^
Weight (kg), Mean (SD)	77.9 (15.66)	77.9 (15.71)	77.5 (15.49)	0.934^	77.6 (14.44)	77.8 (13.21)	77.3 (15.69)	0.872*
APACHE II score, Median (Q1,Q3)	15.0 (11, 25)	16.0 (11, 25)	14.0 (12, 26)	0.457^	13.0 (11, 21)	13.0 (10, 20)	14.0 (12, 26)	0.327^
SOFA score, Median (Q1,Q3)	5.0 (3.00, 8.00)	5.0 (3.00, 8.00)	4.(3, 9)	0.504^	4.0 (3, 8)	5.0 (3, 8)	4.0 (3, 9)	0.689^
Early use of systemic corticosteroids within 24 hours of admission, n (%)	259 (71.5)	216 (69.5)	43 (84.3)	**0.03^^**	77 (82.8)	37 (80.4)	40 (85.1)	0.550^^
Prone status, n (%)	81 (23.3)	66 (22.1)	15 (30.0)	0.224^^	24 (26.7)	9 (20.5)	15 (32.6)	0.192^^
Estimated glomerular filtration rate (eGFR) Baseline, Median (Q1,Q3)	63.0 (32, 87)	62.0 (31, 86)	68.5 (34.00, 96.00)	0.179^	68.0 (38, 95)	70.0 (40.50, 91)	68.0 (34, 96)	0.930^
Acute Kidney Injury (AKI) Within 24 hours of ICU admission, n (%)	114 (32.5)	102 (33.9)	12 (24.0)	0.166^^	23 (24.7)	11 (23.9)	12 (25.5)	0.856^^
Mechanical Ventilation within 24 hours of ICU admission, n (%)	266 (73.9)	232 (75.1)	34 (66.7)	0.205^^	66 (71)	35 (76.1)	31 (66)	0.282^^
Inotropes/vasopressors use within 24 hours of admission) , n (%)	89 (25.1)	77 (25.4)	12 (23.5)	0.774^^	23 (24.7)	11 (23.9)	12 (25.5)	0.856^^
Lactic acid Baseline, Median (Q1,Q3)	1.7 (1.30, 2.30)	1.8 (1.31, 2.33)	1.6 (1.20, 2)	0.165^	1.7 (1.27, 2.2)	1.7 (1.31, 2.23)	1.5 (1.2, 2)	0.353^
Platelets count Baseline, Median (Q1,Q3)	236.0 (178, 302)	234.5 (176.5, 300.5)	243.0 (198, 331.)	0.390^	251.5 (186., 307.5)	262.0 (188, 321)	240.0 (183, 304)	0.761*
Total WBC Baseline, Median (Q1,Q3)	9.5 (6.87, 12.90)	9.6 (6.86, 12.95)	9.2 (6.99, 12.60)	0.519^	9.5 (6.53, 12.71)	10.6 (6.53, 13.00)	9.1 (6.47, 11.90)	0.216^
International normalized ratio (INR), Median (Q1,Q3)	1.1 (1.04, 1.25)	1.1 (1.04, 1.25)	1.1 (1.05, 1.20)	0.523^	1.1 (1.04, 1.25)	1.1 (1.04, 1.32)	1.1 (1.05, 1.17)	0.472^

activated partial thromboplastin time (aPTT) Baseline, Median (Q1,Q3)	30.7 (27.4, 34.9)	30.9 (27.40, 35.40)	30.1 (27.90, 33.30)	0.334^	30.3 (26.95, 34.00)	29.9 (26.80, 34.00)	30.5 (28.10, 33.90)	0.8^
Total bilirubin, Median (Q1,Q3)	9.0 (6.6, 12.95)	9.0 (6.6, 12.5)	9.7 (6.3, 14.3)	0.511^	9.6 (7.1, 14.)	9.5 (7.5, 11.60)	9.7 (6.50, 14.80)	0.768^
Albumin Baseline, Median (Q1,Q3)	31.0 (28.00, 35.00)	32.0 (28, 35.)	30.0 (27, 34)	0.157^	31.0 (28, 35.5)	33.0 (29., 36)	30.0 (27, 34)	0.063^
Alanine aminotransferase (ALT) , Median (Q1,Q3)	34.0 (23, 56)	33.5 (23, 55.5)	38.0 (24.00, 64.00)	0.576^	37.0 (22.00, 66.00)	35.0 (20.00, 72.00)	38.0 (24, 64)	0.931^
Aspartate aminotransferase (AST) , Median (Q1,Q3)	51.0 (35, 80)	51.0 (35, 80)	54.0 (38.00, 88.00)	0.573^	48.5 (36.00, 77.00)	48.0 (34.00, 77.00)	50.0 (38, 85)	0.812^
Creatine phosphokinase (CPK) baseline (U/l), Median (Q1,Q3)	139.0 (68., 378.)	136.5 (71., 361)	174.0 (58, 483)	0.834^	164.0 (69.00, 459.50)	144.0 (72, 361.)	174.0 (58., 563)	0.926^
C-reactive protein (CRP) baseline (mg/l)m Median (Q1,Q3)	119.0 (48., 189.)	105.0 (37.25, 182)	161.0 (71, 199)	**0.049**^	137.0 (71, 182)	128.5 (63, 182)	159.5 (74.00, 186.45)	0.506^
Procalcitonin (ng/ml), Median (Q1,Q3)	0.4 (0.14, 1.26)	0.4 (0.16, 1.20)	0.4 (0.12, 1.50)	0.714^	0.4 (0.13, 1.50)	0.4 (0.20, 1.77)	0.4 (0.13, 0.99)	0.397^
Fibrinogen Level baseline (gm/l), Median (Q1,Q3)	5.2 (3.96, 7.02)	5.2 (4, 7.01)	5.4 (2.53, 7.27)	0.438*	4.9 (2.53, 7.02)	4.9 (2.58, 7.02)	5.0 (2.47, 7.10)	0.788*
D-dimer Level baseline, Median (Q1,Q3)	1.7 (0.88, 3.90)	1.7 (0.88, 3.90)	1.9 (0.85, 3.66)	0.868^	1.7 (0.91, 3.07)	1.5 (0.95, 3.07)	1.7 (0.85, 2.72)	0.798^
Ferritin Level baseline, Median (Q1,Q3)	636.6 (314, 1388)	565.6 (293.80, 1295.00)	1052.5 (648.85, 1887.00)	**0.007^**	805.2 (433.40, 1487)	555.2 (383.6, 1295)	992.9 (648.85, 1689)	0.065^
Blood glucose level Baseline Within 24 hours of ICU admission, Median (Q1,Q3)	11.8 (8.3, 15.3)	12.0 (8.4, 15.40)	11.1 (8.1, 14.85)	0.451^	11.1 (8.1, 15.7)	11.1 (8.6, 17.1)	11.0 (7.8, 14.85)	0.517^
PaO2/FiO2 ratio within 24 hours of admission, Median (Q1,Q3)	83.9 (59.9, 130.6)	82.5 (59.78, 136.1)	89.2 (61.12, 124.)	0.920^	84.6 (59.33, 116.5)	79.2 (59.25, 109.8)	87.0 (61.12, 119.8)	0.622^
Respiratory Rate (RR) Baseline	26.0 (22, 32)	26.0 (22, 32)	28.0 (21.00, 32.00)	0.757^	25.0 (20.50, 30.00)	24.0 (20.00, 29.00)	28.0 (21., 32.)	0.102^
Maximum body temperature Baseline	37.2 (37.00, 37.80)	37.2 (37, 37.9)	37.1 (36.90,	0.127^	37.2 (37, 37.60)	37.2 (37, 37.7)	37.1 (37, 37.5)	0.147^

			37.50)					
Patient received nephrotoxic drugs/material during ICU stay	294 (82.4)	251 (82.0)	43 (84.3)	0.691^^	80 (87)	41 (91.1)	39 (83.0)	0.247^^
Comorbidity, n(%)								
Atrial fibrillation (A Fib)	16 (4.4)	12 (3.9)	4 (7.8)	0.2**	6 (6.5)	2 (4.3)	4 (8.5)	0.414**
Heart Failure	54 (14.9)	46 (14.8)	8 (15.7)	0.868^^	11 (11.8)	4 (8.7)	7 (14.9)	0.354^^
Hypertension (HTN)	256 (70.7)	222 (71.4)	34 (66.7)	0.492^^	65 (69.9)	35 (76.1)	30 (63.8)	0.2^^
Diabetes mellitus (DM)	247 (68.2)	218 (70.1)	29 (56.9)	0.06^^	59 (63.4)	34 (73.9)	25 (53.2)	**0.038^^**
Dyslipidemia (DLP)	96 (26.5)	83 (26.7)	13 (25.5)	0.857^^	31 (33.3)	19 (41.3)	12 (25.5)	0.106^^
Chronic kidney disease (CKD)	65 (18)	59 (19)	6 (11.8)	0.214^^	14 (15.1)	9 (19.6)	5 (10.6)	0.228^^
Ischemic heart disease (IHD)	45 (12.4)	42 (13.5)	3 (5.9)	0.126^^	8 (8.6)	6 (13.0)	2 (4.3)	0.13**
Chronic obstructive pulmonary disease (COPD)	10 (2.8)	9 (2.9)	1 (2.0)	0.706**	3 (3.2)	2 (4.3)	1 (2.1)	0.544**
Asthma	17 (4.7)	16 (5.1)	1 (2.0)	0.319**	3 (3.2)	2 (4.3)	1 (2.1)	0.544**
Cancer (any type)	10 (2.8)	8 (2.6)	2 (3.9)	0.585**	3 (3.2)	1 (2.2)	2 (4.3)	0.57**
Deep Vein Thrombosis (DVT)	4 (1.1)	4 (1.3)	0 (0.0)	0.415**	1 (1.1)	1 (2.2)	0 (0)	0.31**
Pulmonary Embolism (PE)	3 (0.8)	2 (0.6)	1 (2.0)	0.336**	1 (1.1)	0 (0)	1 (2.1)	0.32**
Liver disease (any type)	9 (2.5)	8 (2.6)	1 (2.0)	0.8**	3 (3.2)	2 (4.3)	1 (2.1)	0.544**
Stroke	35 (9.7)	31 (10.0)	4 (7.8)	0.634**	9 (9.7)	5 (10.9)	4 (8.5)	0.7**

*T Test / ^ Wilcoxon rank sum test is used to calculate the P-value.
^^ Chi square/ ** Fisher's Exact teat is used to calculate P-value.

Table 2: Regression Analysis for the Outcomes after Propensity Score matching

Outcomes	Crude Analysis		P-value ^^	Hazard Ratio (HR) (95%CI)	P-value $
	Control	Tocilizumab			
In-hospital mortality, n(%)§	31 (67.4)	17 (37.8)	0.005	0.41 (0.22, 0.76)	0.005
30-day mortality, n(%)§	26 (56.5)	16 (34.8)	0.04	0.66 (0.35, 1.24)	0.19
			P-value ^	**beta coefficient (Estimates) (95%CI)**	**P-value** $*
Ventilator free days, Mean (SD) §	8.8 (12.5)	12.3 (13.3)	0.17	0.32 (-0.70, 1.34)	0.54
ICU Length of Stay (Days), Median (Q1, Q3) &	10.0 (3.00, 15.00)	12.5 (8.00, 18.00)	0.37	0.36 (-0.17, 0.89)	0.18
Hospital Length of Stay (Days), Median (Q1, Q3) &	25.0 (10.00, 40.00)	22.0 (14.50, 36.00)	0.84	0.20 (-0.30, 0.71)	0.43

§ Denominator of the percentage is the total number of patients

& Denominator is patients who survived.

^^ Chi-square test is used to calculate the P-value.

^ Wilcoxon rank sum test is used to calculate the P-value.

$ Cox proportional hazards regression analysis is used to calculate hazard ratio (HR) and p-value.

$* Generalized linear model is used to calculate beta coefficient (estimates) and p-value.

Table 3: Regression Analysis for ICU Complication (s) and Supportive Measure (s) after Propensity Score Matching

Outcomes	Crude Analysis	P-value ^^	Odds Ratio (OR)	P-value *^

	Control	Tocilizumab		(95%CI)	
Acute Kidney Injury, n(%)§	28 (60.9)	24 (51.1)	0.34	0.66 (0.29, 1.52)	0.33
Liver Injury, n(%)§	5 (10.9)	4 (8.5)	0.70**	0.76 (0.19, 3.04)	0.69
Respiratory Failure Requiring MV, n(%)	41 (89.1)	34 (72.3)	**0.04**	0.32 (0.10, 0.98)	**0.04**
Inotropes/vasopressors use during ICU stay as supportive measures, n(%)§	30 (69.8)	27 (57.4)	0.23	0.87 (0.38, 1.98)	0.74
Secondary fungal infection, n(%)§	8 (24.2)	9 (23.7)	0.96	0.93 (0.30, 2.86)	0.89

§ Denominator of the percentage is the total number of patients

^^Chi-square /**Fisher Exact test is used to calculate the P-value.

*^Multivariate logistic regression analysis is used to calculate Odds ratio and p-value.